FIND

INTRODUCTION TO REGULATORY

Michelle Zaharik

TOPICS

1. **The purpose of (IVD) regulation**
2. Introduction to established regulatory authorities
3. Conformity assessments, regulatory submissions and technical documentation
4. Risk-based classification of IVDs

WHY WE REGULATE

Main aim of Regulation is to keep Unsafe Products Off the Market

Role of regulation is to promote and protect public health

Regulation is rooted in core ethical principles (mitigate risk of harm to people while maximizing social benefit)

INTRODUCTION TO REGULATORY

HISTORY OF REGULATION

Key Milestones and Countries:

1976

USA: Medical Device Amendments Act

The FDA introduced the first comprehensive framework for medical devices, including IVDs.

1993

EU: In Vitro Diagnostic Directive (IVDD 98/79/EC)

The FDA introduced the first comprehensive framework for medical devices, including IVDs.

1998

Canada: Health Canada Medical Devices Regulations (MDR)

Implemented to address issues specific to the regulation of Medical Devices and IVDs.

2002

Japan: PMDA (Pharmaceuticals and Medical Devices Agency)

Japan forms the PMDA to regulate medical devices, including IVDs.

2012

Australia: Therapeutic Goods Administration (TGA) IVD Regulatory Framework

Introduction of IVD-specific regulatory guidelines.

2017

EU: In Vitro Diagnostic Regulation (IVDR 2017/746)

A significant shift in the EU, replacing the IVDD, with stricter rules and risk-based classification.

2020

China: National Medical Products Administration (NMPA) Guidance

China implements a revised regulatory framework for medical devices and IVDs.

2021

UK: Post-Brexit MHRA Guidelines

The UK introduces its own IVD regulatory framework after leaving the EU, diverging from the CE mark in favor of the UKCA mark.

2022

India: CDSCO IVD Regulations IVDs

India's Central Drugs Standard Control Organization (CDSCO) formalizes IVD regulations under new guidance.

Based on similar fundamentals: *evaluating product quality and product safety* to **Keep Unsafe Products Off the Market**

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REGULATORY AUTHORITIES

WHAT IS A REGULATORY AUTHORITY?

It is a government body or other entity that has the **legal right to control the use or sale** of medical devices within its jurisdiction.

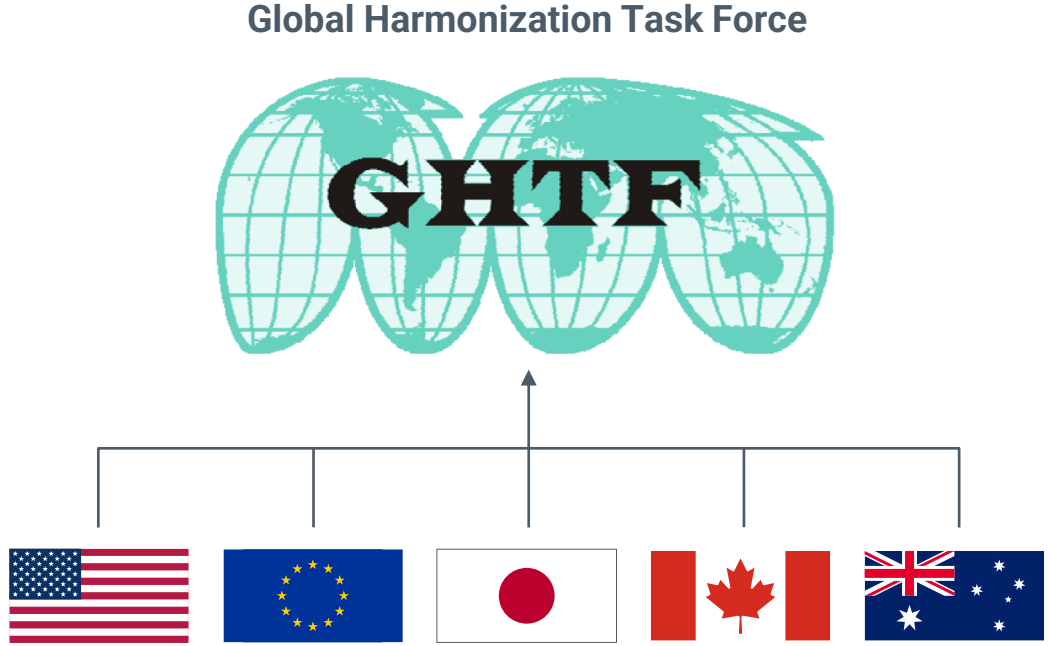
WHAT CAN IT DO?

It may take **enforcement action** (e.g. can stop a device being imported into a country or being sold within a country) to make sure the medical devices marketed within its jurisdiction comply with legal requirements.

GHTF AND IMDRF – PROMOTING HARMONIZATION

- Today's regulatory landscape has been greatly influenced by a regulatory harmonization initiative known as the **Global Harmonization Task Force (GHTF):**

  - Founded in 1992
  - Voluntary group of medical device regulatory authorities and medical device industry members
  - Goal was to standardize medical device regulation across the world
  - Five founding members ("The GHTF Big Five"): Canada, USA, Australia, Japan, and the EU
  - Disbanded in late 2012, replaced by IMDRF



GHTF AND IMDRF – PROMOTING HARMONIZATION

International Medical Device Regulators Forum (IMDRF):

- Successor organization , established in 2011, that includes officials from regulatory agencies (NOT industry) across the world
- Aim is to continue to standardize global medical device regulations by the exchange of information
- Produce harmonized guidance documents based on basic regulatory practices which can then be adopted/implemented by member national regulatory authorities

INTRODUCTION TO REGULATORY

HIERARCHY OF REGULATORY REQUIREMENTS IN ESTABLISHED MARKETS

The Law/Legislative Act

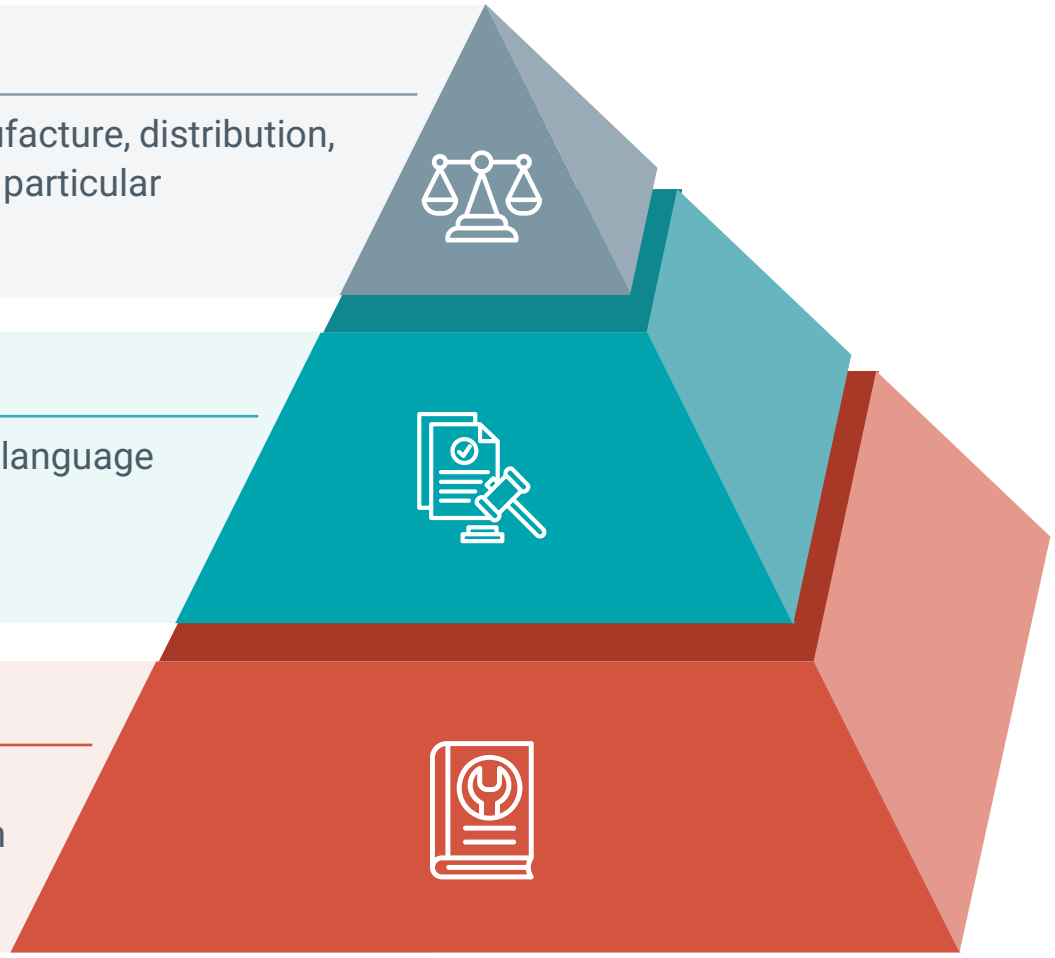
- Sets out the legal requirements for the manufacture, distribution, import and export of medical devices in that particular jurisdiction.

The Regulations

- Translate the legal requirements in a more accessible language and in more detail.

Guidelines and technical standards

- Provide guidance on how to apply the regulations. Although guidelines and standards are generally voluntary, complying with them usually provides presumption of conformity in most situations.



GHTF HIERARCHY OF REGULATIONS: FOCUS ON IVDS

GHTF	US	Australia	Canada	Japan	EU
	FDA	TGA	Health Canada	PMDA/MHLW	(Notified Bodies)
ACT	Federal Food, Drug and Cosmetic Act (FD&C Act)	Australian Therapeutic Goods Act	Food and Drugs Act	Pharmaceutical and Medical Device (PMD) Act	EU IVD Regulation 2017 (IVDR)
REGULATION	Code of Federal Regulations (CFR), in particular Parts 800 to 1299	Therapeutic Goods (Medical devices) Regulations of 2002	Medical Devices Regulations	Cabinet Ordinances, which are superior to the Ministerial Ordinances and Ministerial Notifications	National laws
GUIDANCE/ TECHNICAL STANDARDS	FDA Good Guidance Practice (GGP) documents, Blue Book Memos, Recognized Consensus Standards	Australian Regulatory Guidelines for Medical Devices (ARGMD) medical device standards orders (MDSO) and conformity assessment standards orders (CASO)	Guidelines (also referred to as guidance documents or directives) TPD List of recognized national and international standards for medical devices	Other notifications and administrative notices	MDCG guidance Harmonised standards

- IVD pathways are separated from medicines and vaccines but are often are grouped with medical devices.
- Evolved to balance the ever-increasing number of devices with the limited capacity of regulatory agencies, and to ensure that potential harm to patients remains uncompromised.

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REGULATORY SUBMISSIONS AND CONFORMITY ASSESSMENT (CA)

WHAT IS A REGULATORY SUBMISSION?

Packages of technical documentation (i.e. information and data) required by a Regulatory Authority to determine whether a regulated product (drug, device etc.) is safe and effective for marketing.

WHAT IS A CONFORMITY ASSESSMENT?

The systematic and ongoing examination of evidence and procedures (included in the regulatory submission) to ensure that a medical device (including IVD medical devices) is safe and effective. CA must be carried out within the context of the established regulatory requirements for each specific Regulatory Authority (RA). The CA is the primary focus of a regulatory submission.

RESPONSIBILITIES

- The medical device manufacturer assembles the technical documentation for conformity assessment and provides it to the RA as part of a regulatory submission.
- Both the process and conclusions of the CA will be reviewed by the RA and/or a Conformity Assessment Body (CAB) in the countries and regions where the device is intended to be sold.
- The RA may perform the conformity assessment themselves or may contract a third-party organization to do the assessment for them.

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CONFORMITY ASSESSMENT (CA)

PRE-MARKET CONFORMITY ASSESSMENT

- Required by a Regulatory Authority (RA) to ensure the device is safe and effective and may be placed on the market.

  If the CA is favourable, the RA issues a letter or certificate of approval for the device to be marketed in the jurisdiction.

POST-MARKET CONFORMITY ASSESSMENT

- In most cases, once a device is on a market, it can stay on the market until it is made obsolete/no longer produced or supported by the manufacturer.

  Post-market CA are often triggered by safety concerns and may be device-specific (e.g. resulting from identified changes to the device or concerns about performance), or an entire class of devices.

  If the CA is not favourable, importation/sale may be suspended until changes have been made to improve safety; worst case the device must be withdrawn from the market.

REGULATORY SUBMISSION

DOCUMENTATION SUBMITTED FOR A CONFORMITY ASSESSMENT

- All regulatory submissions require some form of documentation
- High risk submissions require an **assessment of your QMS**.
  - A well-implemented QMS is essential for maintaining control over device design, development, manufacturing and post-market activities, which is part of the required documentation.
- The bulk of a submission is the **Technical Documentation** for a device and an explanation of how the Technical Documentation demonstrates that the device conforms with (meets) essential principles of safety and performance and other relevant regulatory requirements and guidelines
- **Good documentation is key** to demonstrating compliance with global standards and maintaining accurate and comprehensive records is key to a successful regulatory strategy.

TECHNICAL DOCUMENTATION

Key pieces of technical documentation include:

- Evidence of design planning and design control
- Manufacturing information
- Risk management activities/risk assessments
- Verification and Validation study protocols and reports

RECOMMEND TO USE IMDRF IVD TOC TO BUILD TECHNICAL DOCUMENTATION:

1. Chapter 1 – Regional Administrative 15
2. Chapter 2 – Submission Context 35
3. Chapter 3 – Analytical performance and other evidence 60
4. Chapter 4 – Clinical evidence 105
5. Chapter 5 – Labelling and promotional material 114
6. Chapter 6 – Quality management system 121
7. Document revision history 139

RECOMMEND TO USE IMDRF IVD TOC TO BUILD TECHNICAL DOCUMENTATION:

3 Chapter 3 – Analytical performance and other evidence

Row ID	Regions & Level		Heading	Common Content	Regional Content
3.01	IMDRF	1	Chapter Table of Contents	a) Includes major headings for the chapter, to the level of the custom headings. b) Specifies the page number for each item referred to in the table.	
3.02			Chapter Retired		
3.03			Chapter Retired		
3.04			Chapter Retired		
3.04.01			Chapter Retired		
3.04.02			Chapter Retired		
3.05	IMDRF	1	Analytical Performance	**NO CONTENT AT THIS LEVEL**	
3.05.01	IMDRF	2	Stability of Specimen(s)	Information regarding and studies to support the stability, storage and where appropriate, transport, of all of the specimen type(s) identified in the labelling, including any and all recommended additives (e.g. anticoagulants) is to be provided in this section. This should include:	**EU** For specific IVDR requirements see IVDR Annex II Section 6.1.1.

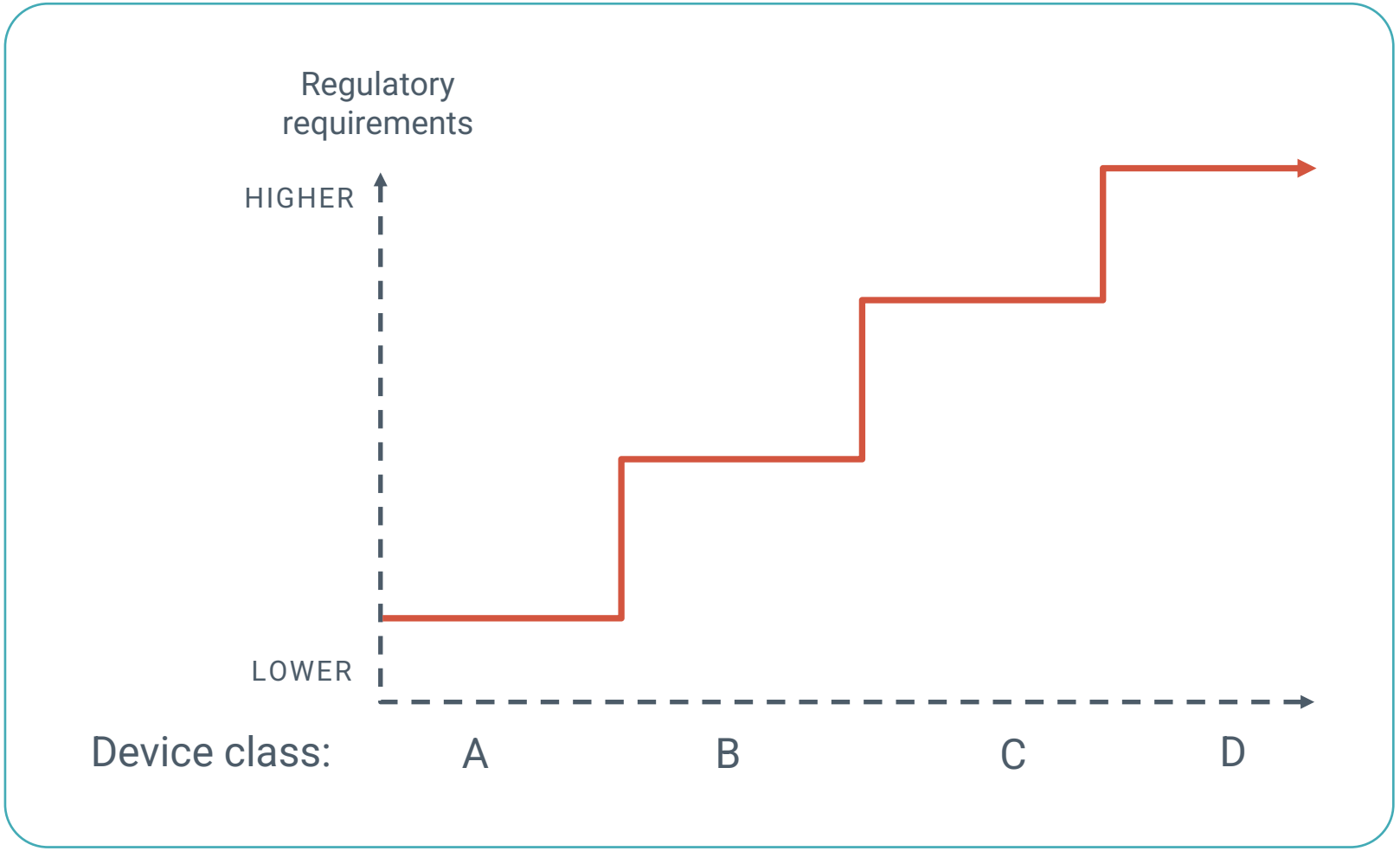
Also recommend to refer to the IMDRF Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices, which describes fundamental design and manufacturing requirements needed to ensure a device is safe and performs as intended throughout its product lifecycle.

TECHNICAL DOCUMENTATION

The amount of documentation (objective evidence) needed in the technical file is

based on the Risk Classification and the novelty of the device.

Higher risk/novelty = larger number of studies required = more documentation is needed.



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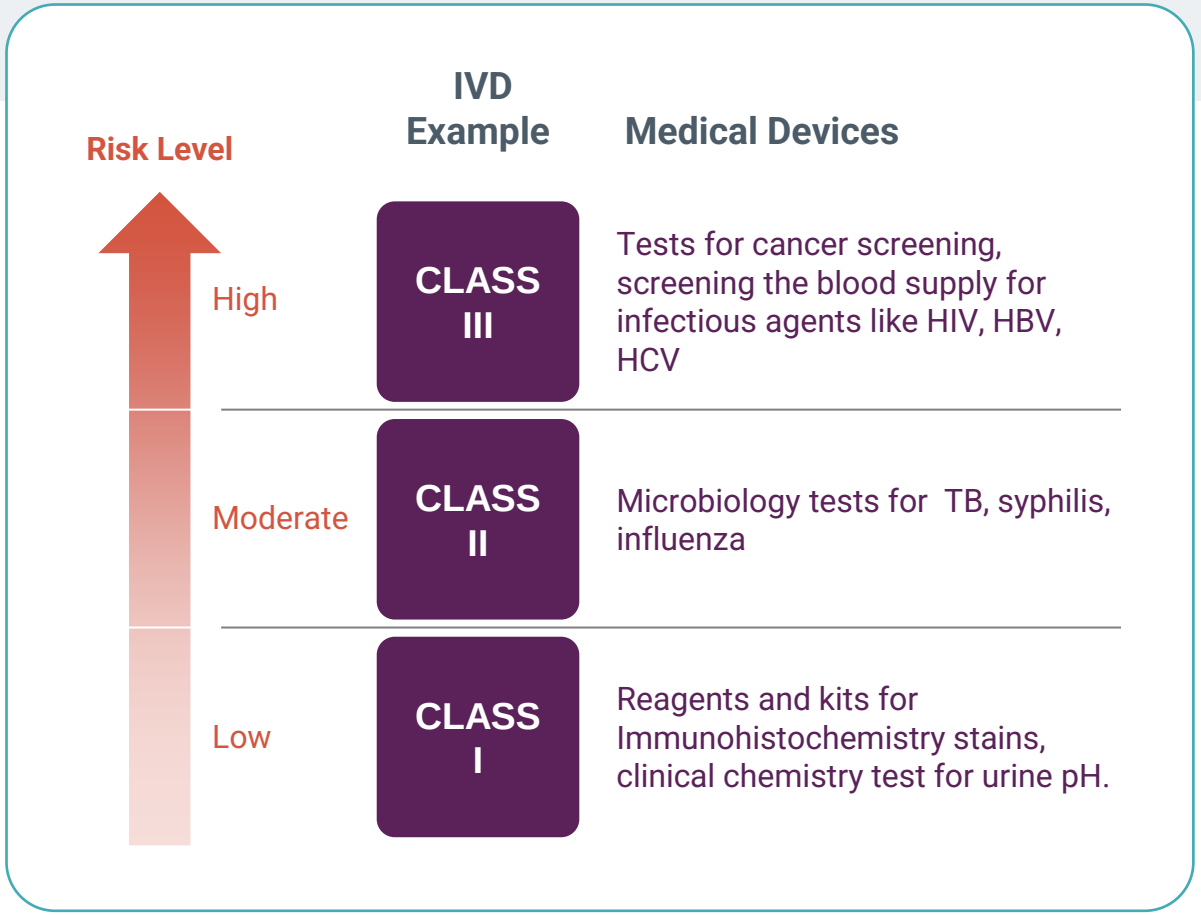
RISK BASED CLASSIFICATION – TWO DIFFERENT PHILOSOPHIES

Nomenclature Based Classification

Nomenclature based classification

- The early device regulations established a nomenclature-based classification system.
- Known, pre-determined categories of devices were assigned a risk classification - **low, medium or high**.
- The regulator assigns a level of regulatory scrutiny (or regulatory controls) directly proportionate with their risk class.
- Used in the **US and Japan**.

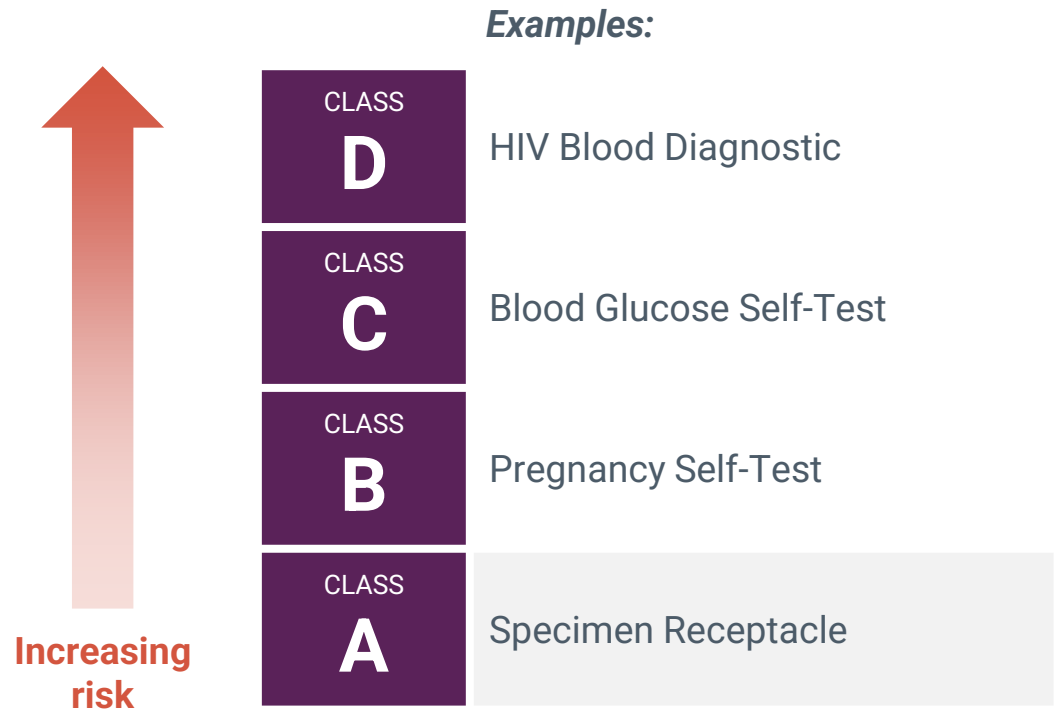


RISK BASED CLASSIFICATION – TWO DIFFERENT PHILOSOPHIES

Generic Classification Rules

- Use of a set of generic rules that can be applied to any IVD to determine its risk classification based on the potential for harm to the patient or the user, and to public health.
- 4 risk classes: **low, low to medium, medium to high and high risk** (Classes A - D respectively).
- The classification philosophy recommended by the GHTF and later other harmonization initiatives, and adopted by the regulatory authorities in the **EU, Australia and Canada**, as well as by the **ASEAN Medical Devices Directive**. It is also endorsed by **WHO**.

In vitro diagnostic medical devices



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RISK BASED CLASSIFICATION

Level of risk	USA FDA	Australia TGA	Canada Health Canada	Japan PMDA/MHLW	EU Notified Body	IMDRF/ WHO
Low or no public health risk and/or low individual risk	Class I (low)	Class 1 IVD	Class I	Class I (low risk)	Class A	Class A
Low public health risk and/or moderate individual risk	Class II (moderate)	Class 2 IVD	Class II	Class II (low risk)	Class B	Class B
Moderate public health risk and/or high individual risk		Class 3 IVD	Class III	Class III (high risk)	Class C	Class C
High public health risk and/or high individual risk	Class III (high)	Class 4 IVD	Class IV		Class D	Class D

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IMPACT OF INTENDED USER ON RISK CLASSIFICATION

Risk classification increases the farther outside the clinical laboratory the test is to be used; centers on the training of the intended user

Intended Use Setting	Intended User	IMDRF/ WHO	USA (FDA)	Australia (TGA)	Canada (Health Canada)	Japan (PMDA/MHLW)	EU (Notified Body)
Hospitals / Laboratories	Laboratory technician	Risk classification of the device	Risk classification of the device	Risk classification of the device	Risk classification of the device	Risk classification of the device	Risk classification of the device
Primary Care	Trained health care professional (nurse, doctor)	Class C unless modified by risk class of device (e.g. HIV ST Class D; pregnancy urine test Class B)	Additional studies with untrained users; CLIA Waiver	Risk classification of the device; studies take into consideration the intended user	Near Patient IVD = Class III "For professional use only"		Risk classification of the device; studies take into consideration the intended user
At home / community	Self-testing – lay user Pharmacist Community health workers		Additional studies required with lay users "For Over-the-Counter Use"	Class 3	Near Patient IVD = Class III unless modified by risk class of device (e.g. HIV ST Class IV) "For home use"		Class C unless modified by risk class of device (e.g. HIV ST Class D; pregnancy urine test Class B)

GLOBALLY RECOGNISED REGULATORY PREMARKET PATHWAYS ACCORDING TO RISK CLASS

	A	B	C	D
	↓	↓	↓	↓
Preparatory stage: collecting evidence of the safety and performance of the medical device	Device classification is determined according to the classification rules.			
	↓	↓	↓	↓
	Registration of establishment (manufacturer, authorized representative and/or importer or distributor)*			
	↓	↓	↓	↓
	Preparation and maintenance of the technical documentation according to requirements			
	Evidence of effective implementation of QMS and declaration of conformity	ISO 13485 certificate or inspection/audit from an accredited organization is required		
	↓	↓	↓	↓
Market authorization procedure	Listing submission to the regulatory authority	Submission of technical documentation/dossier to the Authority/CAB (including clinical evidence and evaluation)		
	↓	↓	↓	↓
	Usually**, no review is required. Only notification to the regulatory authority is required.	Usually, administrative review only	Technical review	In-depth technical review
		Review is conducted, including a technical and administrative review. Novel and high-risk products may also be subject to an Expert Panel consultation.		
	↓	↓	↓	↓
				In-depth review of clinical evidence (may require clinical investigation)
	↓	↓	↓	↓
Approval	NRA lists the medical device	NRA issues market authorization when all requirements are fulfilled or sends notice of deficiencies or rejection.		

* Overseas manufacturer shall assign an authorized representative

** Except for Class A devices that are sterile or have a measuring function: regulatory audit can be considered.

WHO Global Model Regulatory Framework for medical devices including in vitro diagnostic medical devices, Annex 3

KEY TAKEAWAYS

1

Regulation should not be seen as a barrier to market entry, but recognized for its role in promoting and protecting public health.

2

Extent of conformity assessments are based on risk posed by the device to the individual or to public health, which determine the amount of technical documentation needed to support device safety and performance that must be included in a regulatory submission.

3

Familiarity with the IMDRF Table of Contents, the IMDRF Essential Principles, and regulatory pathways for “The GHTF Big 5” is an excellent starting point for understanding how to show your device is safe and performs as expected and will improve chances of a smooth pathway to regulatory approval.

FIND

QUESTIONS & FEEDBACK